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# Using a genetic, observational study as a strategy to estimate the potential cost-effectiveness of pharmacological CCR5 blockade in dialysis patients

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***Background and objective*** **Randomized clinical trials are expensive and time consuming. Therefore, strategies are needed to prioritise tracks for drug development. Genetic association studies may provide such a strategy by considering the differences between genotypes as a proxy for a natural, lifelong, randomized at conception, clinical trial. Previously an association with better survival was found in dialysis patients with systemic inflammation carrying a deletion variant of the CC-chemokine receptor 5 (CCR5). We hypothesized that in an analogous manner, pharmacological CCR5 blockade could protect against inflammation-driven mortality and estimated if such a treatment would be cost-effective.**

***Methods*** **A genetic screen and treat strategy was modelled using a decision-analytic Markov model, in which patients were screened for the CCR5 deletion 32 polymorphism and those with the wild type and systemic inflammation were treated with pharmacological CCR5 blockers. Kidney transplantation and mortality rates were calculated using patient level data. Extensive sensitivity analyses were performed.**

***Results*** **The cost-effectiveness of the genetic screen and treat strategy was €18 557 per life year gained and €21 896 per quality-adjusted life years gained. Concordance between the genetic association and pharmacological effectiveness was a main driver of cost-effectiveness. Sensitivity analyses showed that even a modest effectiveness of pharmacological CCR5 blockade would result in a treatment strategy that is good value for money.**

***Conclusion*** **Pharmacological blockade of the CCR5 receptor in inflamed dialysis patients can be incorporated in a potentially cost-effective screen and treat programme. These findings provide formal rationale for clinical studies. This study illustrates the potential of genetic association studies for drug development, as a source of Mendelian randomized evidence from an observational setting.** ***Pharmacogenetics and Genomics*** **21:417–425 © 2011 Wolters Kluwer Health | Lippincott Williams & Wilkins.**

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## Introduction

Pharmacological interventions that are of benefit in nondialysis populations have thus far been disappointing in dialysis patients, underscoring the need for novel intervention strategies, specifically targeted at the dialysis population [1,2]. However, development of novel pharmacological approaches followed by randomized clinical trials is expensive and time consuming, providing an immense obstacle to the development and introduction of innovative approaches in patient care. Research and development costs for a single approved cardiovascular drug can reach hundreds of millions of dollars, with most costs accrued in phase II and III trials [3]. Therefore, alternative strategies are urgently needed to facilitate the multifaceted process from drug development to introduction in clinical practice. Observational studies using genetic variants might provide such a strategy [4]. Given the random assignment of alleles in gamete formation, genetic variants can be considered to mimic the randomization process of randomized clinical trials. Data obtained through genetic association studies could therefore be considered a type of natural, lifelong, clinical trial, with genetically different groups being randomized at conception, hereby limiting confounding. This approach is known as Mendelian randomization [5,6].

One of the main driving forces in the accelerated atherosclerosis in patients with end-stage renal disease (ESRD) is chronic inflammation [7]. This population might therefore benefit from alternative therapies

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directed against the chronic inflammatory response. In this inflammatory process chemokines and chemokine receptors play an important role [8–10]. One of the chemokine receptors involved is the CC-chemokine 5 receptor (CCR5). Animal data show that pharmacologic intervention in the CCR5 chemokine pathway reduces atherosclerosis [11–13]. The relevance of these findings for humans is supported by genetic association studies on the CCR5 deletion 32 (CCR5Δ32) polymorphism, leading to functional CCR5 deficiency [14]. These studies show that CCR5Δ32 is associated with better outcome in different populations [15–18]. Previously, we found that CCR5Δ32 was associated with protection against mortality in a Dutch cohort of dialysis patients characterized by inflammation and replicated these findings in a Swedish cohort [19]. Taken together, these data suggest that intervention-targeting inflammation, in particular targeting the CCR5, may have the potential to improve prognosis in ESRD [20].

Interestingly, pharmacological blockade of CCR5 is feasible in human as it is applied in clinical practice for treatment of human immunovirus (HIV) infection, which increases the feasibility of development of CCR5 blockade as a treatment strategy for protection against inflammation-driven atherosclerosis in ESRD [21].

In line with the above, genetic association data on long-term outcome in patients with versus without CCR5Δ32 can be considered as a virtual long-term randomized intervention study on pharmacological blockade of the CCR5 receptor providing a fast and cheap simulation setup for a real-life clinical trial. Systematic reviews have shown that pharmacogenetic screen and treat programmes show great potential for developing cost-effective treatment modalities [22,23]. In this analysis, we use these concepts to estimate the potential cost-effectiveness of CCR5Δ32 screening and pharmacological CCR5 blockade in dialysis patients, from the perspective of the Dutch healthcare system.

## Methods

### Patients

For this study we used data from our previously published study on the effect of the CCR5Δ32 polymorphism on inflammation-associated mortality in dialysis patients. This study was part of the NEtherlands COoperative Study on the Adequacy of Dialysis (NECOSAD), a multicenter prospective follow-up study comprising incident (new and consecutive) ESRD patients from 38 Dutch dialysis centres included between July 1998 and December 2001. Detailed descriptions of the study design and results have been published previously [19].

Eligibility criteria for inclusion in the NECOSAD cohort were 18 years or older and no previous renal replacement therapy. All patients gave informed consent and all local medical ethics committees gave their approval. Patients were evaluated at 3 and 6 months after start of dialysis and every 6 months thereafter until death or date of censoring. Censoring involved transfer to a nonparticipating dialysis centre, withdrawal from the study or end of the follow-up period in June 2007. Patients receiving a kidney transplant were not censored; data on their survival were obtained from the Dutch renal registry (RENINE).

### Data collection and clinical definitions

High-sensitivity CRP (hsCRP) was measured by means of particle-enhanced immunonephelometry using a standard CardioPhase hsCRP for BNII (Dade Behring Holding GmbH, Liederbach, Germany; detection limit 0.1 mg/l, precision 0.1 mg/l) [24]. Systemic inflammation was defined as hsCRP concentrations above 10 mg/l. This cutoff point has been used in ESRD patients and has been validated with regard to the prediction of survival of ESRD patients [25]. In addition it was demonstrated that a single measurement of elevated CRP levels was associated with a similar predictive power on mortality as repeated CRP measurements [26].

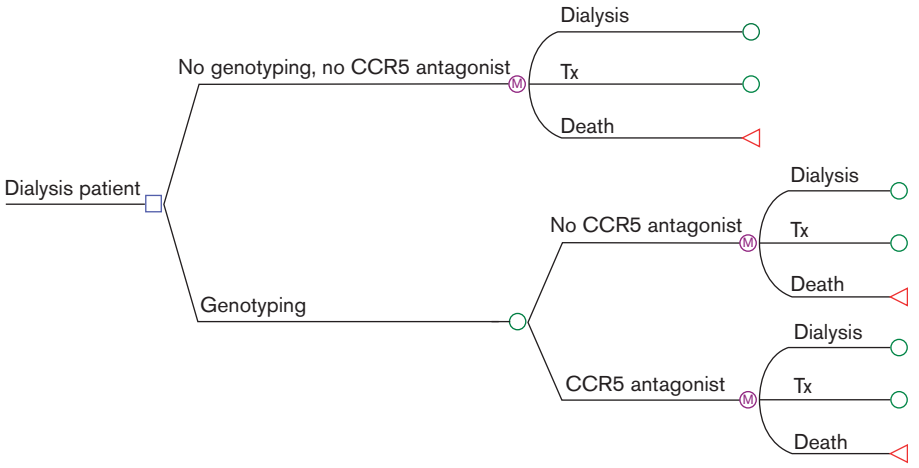
CCR5 genotypes were determined with a PCR-based allelic discrimination assay using primers (Life Technologies Corporation, Carlsbad, California, USA) and allele-specific probes (Life Technologies) as described previously [27].

Patients were divided in four groups based on their CCR5Δ32 genotype and hsCRP level: CCR5 insertion/insertion with low hsCRP (< 10 mg/l), CCR5 ins/ins with high hsCRP (> 10 mg/l), CCR5Δ32 with low hsCRP (< 10 mg/l) and CCR5Δ32 with high hsCRP level (> 10 mg/l). Patients homozygous or heterozygous for the deletion allele were clustered since the presence of one minor allele has been associated with reduced receptor function [14]. Causes of death were classified according to the codes of the European Renal Association – European Dialysis and Transplantation Association [28]. The following codes were used to classify cardiovascular mortality: myocardial ischaemia and infarction; cardiac failure, fluid overload and pulmonary oedema, cardiac arrest, cerebrovascular accident, haemorrhage from ruptured vascular aneurysm, mesenteric infarction, hyperkalaemia, hypokalaemia, cause of death uncertain or unknown.

### Analytical approach

We modelled the potential cost-effectiveness of CCR5Δ32 screening and pharmacological CCR5 blockade using a decision-analytic Markov model (Fig. 1). Markovian modelling is a commonly used technique in decision analyses to handle the complexity of multiple interconnective possible consequences [29]. The health states in our Markov model were haemodialysis (HD), peritoneal dialysis (PD), renal transplantation (Tx) and death. Cohorts of 1000 patients entered the model in the HD

**Fig. 1**




Decision tree and Markov model (M). Transition probabilities of the Markov model are shown in Table 2. Tx, transplantation.

or PD health state and were followed for a time period of 10 years. Clinical data were used to model transition probabilities; patients could receive a kidney transplant, experience renal graft failure and return to dialysis or die. The number of patients in each health state was determined by monthly cycles throughout the entire follow-up period [30].

### Effectiveness of pharmacological CCR5 blockade

Transition probabilities for kidney Tx and mortality were calculated using the patient-level NECOSAD data [19]. Kidney Tx and mortality rates were calculated for the four patient groups. As of small numbers the rate of renal transplant failure was calculated for all four groups combined. Pharmacological CCR5 blockade was assumed to mimic the effects of the Δ32 polymorphism in patients with high inflammation status, thus, improving patient survival in the patient group with the CCR5 insertion/insertion genotype and systemic inflammation up to the level of the patient group with the CCR5Δ32 polymorphism and systemic inflammation. In particular, the relative risk (RR) for pharmacological CCR5 blockade in the inflamed group was calculated using clinical data as 0.61 for all-cause mortality, 0.41 for cardiovascular mortality and 0.80 for noncardiovascular mortality. While the main focus of this analysis was on mortality, we also calculated, based on clinical data, that pharmacological CCR5 blockade improved the probability of renal Tx (RR = 2.41). To reflect our main focus on mortality we performed a separate analysis without modelling an effect on the probability of renal Tx.

### Utilities

Health-related quality of life (QoL) of patients on HD and PD were obtained by interviewing patients participating in the NECOSAD study, detailed inclusion criteria and methods are described elsewhere [31]. QoL of patients in the Dutch NECOSAD study were assessed with the EQ-5D instrument (EuroQol Group, Rotterdam, The Netherlands), which were applied to data from a UK population sample to obtain community based preference data [32]. No QoL-assessment of transplanted patients was performed in NECOSAD patients; these utilities were obtained from a Swedish study [33]. With QoL measurements, cost-effectiveness estimations can be made in terms of costs per quality-adjusted life years (QALY) gained. A commonly cited implicit threshold for treatments that are deemed good value for money is €50 000 per QALY in The Netherlands [34].

### Costs

A third-party healthcare payer perspective was adopted for cost estimates. Healthcare costs were classified into one of two categories: related costs and unrelated future costs [35].

Related costs comprise costs directly related to the strategy under consideration. The cost of the genetic screening test for the CCR5Δ32 polymorphism was based on PCR and included staff costs [36]. The price of hsCRP screening was based on Dutch laboratory prices. Drug costs of pharmacological CCR5 blockade were based on Dutch prices of the CCR5 antagonist Maraviroc 300 mg (Celsentri) once daily [37], including 6% value-added tax and a 3-monthly pharmacists' prescription fee of €600. Costs of cardiovascular mortality were based on national Dutch life tables and healthcare expenditures adjusted for comorbidities [38]. Costs of noncardiovascular death and of Tx graft failure were derived from a study with data from Dutch registries on renal diseases [39].

Unrelated future costs comprised costs that are independent of current spending, apart from the effects of that spending on survival [40,41]. In particular, as dialysis and renal Tx care are not a direct consequence of CCR5 blockade but of the preexisting condition of ESRD; these costs were consistently classified as unrelated future costs. The costs of dialysis and renal Tx were based on data on volumes of recourse use, including consultations, hospitalisations and laboratory services and use of medication obtained from the NECOSAD study [31].

In line with current pharmacoeconomic guidelines, unrelated future costs were not included [35,42]. However, to determine the influence of unrelated future costs, these costs were included in a separate analysis. All costs were updated to 2009 values.

### Discounting rates

Costs were discounted at 4% per annum and health effects at 1.5% per annum, following Dutch guidelines for pharmacoeconomic research [43].

### Sensitivity analyses

Univariate and probabilistic sensitivity analyses and a threshold analysis were performed. In the univariate sensitivity analysis, all model parameters were varied by 25% to determine the main cost and effect drivers in our model. Discount rates were varied to 0 and 3% per annum based on recommendations by Gold *et al.* [44] and Drummond *et al* [35]. The probabilistic sensitivity analysis was performed according to standard methods [29], using 10 000 iterations and included all model parameters, except therapy costs and effectiveness of pharmacological CCR5 blockade which were explored in a threshold analysis. Gamma distributions were assumed for costs and β distributions for utilities [29]. In the absence of data on standard deviations for costs, we assumed 25% of the mean. Uncertainty in mortality and Tx rates was captured by nonparametric bootstrapping of the NECOSAD data, using 10 000 iterations [45]. As equivalence between genetic effects and associated pharmacologic effectiveness is not a given fact [46], a threshold analysis was performed to determine the combined influence of drug effectiveness and treatment costs of pharmacological CCR5 blockade on the cost-effectiveness of the screen-and-treat strategy. The pharmacoeconomic model and sensitivity analyses were constructed using the statistical package R, version 2.5.1 (R Foundation, Vienna, Austria). A graph of the threshold analysis was constructed using Sigmaplot, version 10.0 (SYSTAT Software Inc., Chicago, Illinois, USA).

## Results

### Study population

The study population used for modelling consisted of 413 patients. The CCR5 insertion32/deletion32 polymorphism was distributed as follows: insertion/insertion: 333 (80.6%); insertion/deletion: 73 (17.7%) and deletion/deletion: seven (1.7%). The genotype distribution did not deviate significantly from Hardy–Weinberg equilibrium ($P = 0.21$). Baseline characteristics are shown in Table 1. The patient characteristics for the different genotype groups were similar at the start of dialysis, except antihypertensive medication use. Patients homozygous or heterozygous for the deletion allele used more antihypertensive medications ($P = 0.01$). From the 413 patients included, 225 (55%) had the CCR5 insertion/insertion genotype and low hsCRP levels, 108 (26%) the CCR5 insertion/insertion genotype and high hsCRP levels, 55 (13%) the CCR5Δ32 polymorphism and low hsCRP levels and 25 (6%) the CCR5Δ32 polymorphism and high hsCRP levels.

### Mortality and transplantation rates

Annual transition probabilities without CCR5 antagonist therapy are shown in Table 2. The probability of renal Tx was lower in the patient group with CCR5 insertion/insertion genotype and systemic inflammation compared with the three other patient groups. Cardiovascular and noncardiovascular mortality was higher in the patient group with CCR5 insertion/insertion genotype and systemic inflammation compared with the other patient groups. In the Markov model, pharmacological CCR5 blockade in this patient group improved survival and the probability of renal Tx up to the level of patients with the CCR5Δ32 polymorphism and systemic inflammation (Table 2).

**Table 1 Baseline characteristics**

| | *N*=413 |
|---|---|
| Sex: males | 253 (61.3) |
| Age (years) | 62 (50–71) |
| Caucasian | 379 (91.8) |
| Haemodialysis | 277 (67.1) |
| Peritoneal dialysis | 136 (32.9) |
| Primary kidney disease | |
| Diabetes mellitus | 75 (18.2) |
| Glomerulonephritis | 48 (11.6) |
| Renal vascular disease | 76 (18.4) |
| Other | 214 (51.8) |
| Cardiovascular disease | 144 (34.9) |
| Diabetes mellitus | 105 (25.4) |
| Smoking | |
| Never | 120 (29.2) |
| Former | 194 (47.2) |
| Current | 97 (23.6) |
| DBP (mmHg) | 83 (12.8) |
| SBP (mmHg) | 150 (25.4) |
| Antihypertensive medication | 356 (86.2) |
| Lipid-lowering medication | 121 (29.3) |
| hsCRP (mg/l) | 5.1 (1.9–13.7) |
| hsCRP > 10 (mg/l) | 133 (32.2) |
| Cholesterol (mmol/l) | 5.0 (1.3) |
| Albumin (g/l) | 32.5 (6.9) |
| Hemoglobin (g/dl) | 11.0 (1.4) |
| GFR (ml/min) | 4.2 (3.1) |
| Kt/V/week | 2.3 (0.9) |

CRP, C-reactive protein; DBP, diastolic blood pressure; GRF, glomerular filtration rate; hsCRP, high-sensitivity CRP; SBP, systolic blood pressure.

**Table 2 Annual transition probabilities (95% CI) in the four CCR5Δ32 polymorphism and inflammation status groups without treatment with pharmacological CCR5 blockade [19]**

| | CCR5 insertion/insertion, no inflammation (%) ($n=225$) | CCR5 insertion/insertion, high inflammation[a] (%) ($n=108$) | CCR5Δ32, no inflammation (%) ($n=55$) | CCR5Δ32, high inflammation (%) ($n=25$) |
|---|---|---|---|---|
| Transplantation | 10.9 (8.9–13.4) | 5.1 (3.0–8.4) | 11.2 (7.4–16.8) | 11.8 (6.4–21.5) |
| Transplantation graft failure | 2.2 (1.2–4.0) | 2.2 (1.2–4.0) | 2.2 (1.2–4.0) | 2.2 (1.2–4.0) |
| Cardiovascular mortality | 4.3 (3.2–5.7) | 9.5 (6.8–13.1) | 4.1 (2.3–7.4) | 4.0 (1.5–10.3) |
| Noncardiovascular mortality | 4.4 (3.3–5.8) | 9.7 (7.0–13.4) | 4.5 (2.6–7.8) | 7.8 (4.0–15.1) |

CCR5, CC-chemokine receptor 5; CCR5Δ32, CC-chemokine receptor 5 deletion 32; CI, confidence interval.
[a]In the genotyping strategy of the economic model, patients with the CCR5 insertion/insertion and high inflammation status received CCR5 antagonists; thereby increasing transplantation rates and reducing mortality rates up to the level of patients with the CCR5Δ32 polymorphism and high inflammation status.

**Table 3 Parameters used in the analyses**

| Variable | Baseline value ± SD | Reference |
|---|---|---|
| Costs | | |
| Discounting rate for costs | 4% | [43,47] |
| Related costs[a] | | |
| Genetic screening test | €50 ± 13 | [36] |
| CRP screening test | €21 ± 5 | |
| Drug costs Maraviroc (per year) | €5057 ± 1,264 | [37] |
| Transplantation graft failure | €4581 ± 1,145 | [39] |
| Cause of death | | |
| Myocardial ischaemia and infarction | €2448 ± 612 | [38] |
| Cardiac failure/fluid overload/ pulmonary oedema | €4529 ± 1132 | [38] |
| Cardiac arrest | €2448 ± 612 | [38] |
| Cerebrovascular accident | €5753 ± 1438 | [38] |
| Mesenteric infarction | €3550 ± 888 | [38] |
| Hyperkalaemia | €1224 ± 306 | [38] |
| Cause unknown or cause uncertain[b] | €3469 ± 867 | [38] |
| Noncardiovascular mortality | €2316 ± 579 | [39] |
| Unrelated future costs[a] | | |
| ESRD care costs | | |
| Haemodialysis year 1 | €84 825 ± 21 206 | [31] |
| Haemodialysis later years | €80 482 ± 20 121 | [31] |
| Peritoneal dialysis year 1 | €65 706 ± 16 427 | [31] |
| Peritoneal dialysis later years | €60 985 ± 15 246 | [31] |
| Transplantation year 1 | €52 199 ± 13 049 | [31] |
| Transplantation later years | €10 440 ± 2610 | [31] |
| Health effects | | |
| Discounting rate for health effects | 1.5% | [43,47] |
| Quality of Life | | |
| Haemodialysis | 0.71 ± 0.275 | [31] |
| Peritoneal dialysis | 0.75 ± 0.256 | [31] |
| Transplantation | 0.86 ± 0.133 | [33] |
| Mortality and transplantation probabilities | See Table 1 | [19] |
| Therapy effectiveness (relative risk) | | |
| All-cause mortality | 0.61 | [19] |
| Cardiovascular mortality | 0.41 | [19] |
| Noncardiovascular mortality | 0.80 | [19] |
| Renal transplantation | 2.41 | [19] |

ESRD, end-stage renal disease; SD, standard deviation.
[a]In the absence of data on standard deviations for costs, we assumed 25% of the mean.
[b]Weighted average of all cardiovascular mortality causes.

**Table 4 Cost-effectiveness in the base–case analysis**

| | Costs | Life years | QALY |
|---|---|---|---|
| Standard care | €1863 | 5.71 | 4.36 |
| Screen and treat strategy | €8482 | 6.07 | 4.67 |
| Screen and treat strategy (no Tx effect) | €8460 | 6.07 | 4.63 |
| Cost-effectiveness | | Cost per LYG | Cost per QALY gained |
| Screen and treat strategy | | €18 557 | €21896 |
| Screen and treat strategy (no Tx effect) | | €18 494 | €24642 |

QALY, quality-adjusted life years; Tx, transplantation.

## Cost-effectiveness

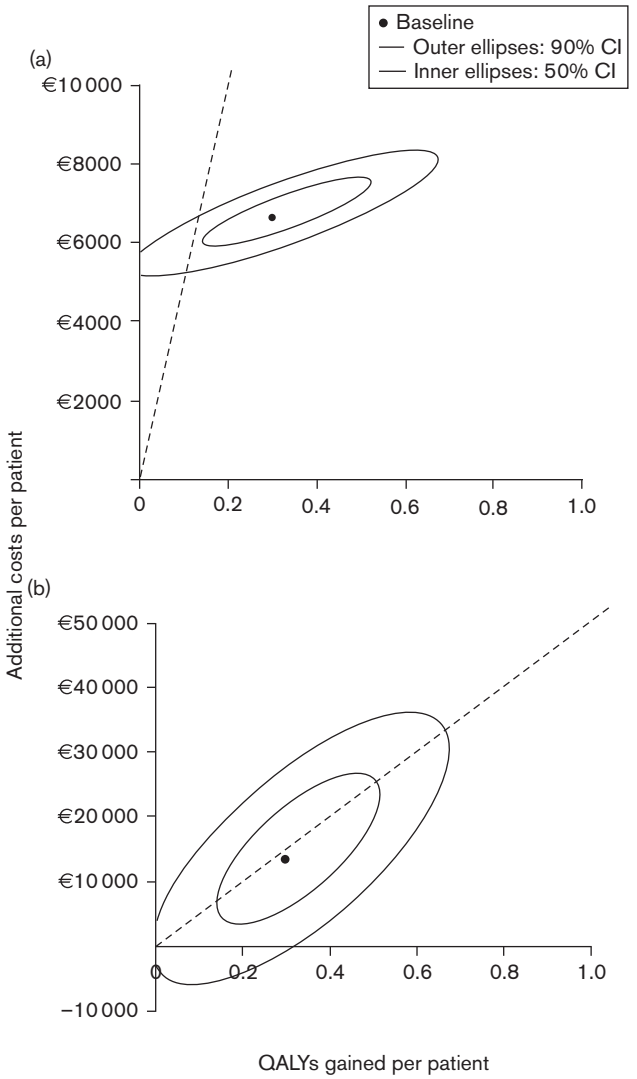
Parameters used for the analyses are shown in Table 3. Screening for the CCR5Δ32 polymorphism and treating patients with the CCR5 insertion/insertion genotype and systemic inflammation with pharmacological CCR5 blockade resulted in an average of 0.36 life years and 0.31 QALYs gained at an expense of €8482 per patient, compared with €1863 per patient in the nonscreening cohort (Table 4). Therefore, the incremental cost-effectiveness ratio (ICER) of the screen and treat strategy compared with not screening was €18 557 per life year gained (LYG) and €21 896 per QALY gained. Results were similar without the model assumption that pharmacological CCR5 blockade improved patients' probability of renal Tx, €18 494 per LYG and €24 642 per QALY gained.

As described, the unrelated future costs of dialysis and Tx care due to improved survival were not included. The aforementioned increased survival of 0.36 life years in the genetically screened cohort, indeed required considerable dialysis costs. These costs were only partly offset by a shift towards less costly renal Tx care in these patients. In total, additional unrelated future costs were €6720 per patient in the screening cohort. When these costs are included, the cost-effectiveness of the selective screen and treat strategy rose considerably to €37 400 per LYG and €44 127 per QALY gained, thus doubling the ICERs for these scenarios.

## Sensitivity and threshold analyses

Results of the probabilistic sensitivity analysis are shown in Fig. 2, demonstrating the uncertainty around the cost-effectiveness estimates of the screen and treat strategy. The increase in cost-effectiveness as well as the uncertainty around these estimates because of including unrelated future costs is evident. In Fig. 2, the solid dot

**Fig. 2**




(a, b) Cost-effectiveness of the screen and treat strategy. (a) Excluding unrelated future costs (end-stage renal disease care costs). (b) Including unrelated future costs. Dotted line denotes the willingness to pay threshold for one quality-adjusted life year at €50 000 [34]. CI, confidence interval; QALY, quality-adjusted life years.

denotes the base–case outcome (using the most likely parameter estimates), whereas the inner and outer ellipses denote the 50 and 90% probability intervals, respectively, around this base–case estimate. Univariate sensitivity analyses showed that the main drivers of the cost-effectiveness of the screen and treat strategy were the costs of pharmacological CCR5 blockade and the effectiveness of pharmacological CCR5 blockers to reduce mortality. The cost-effectiveness was relatively insensitive to plausible variations of the other parameters. These two main parameters were further explored in a threshold analysis, shown in Fig. 3. The red line in this figure denotes the base–case assumptions for drug effectiveness and treatment costs. With decreasing therapy costs and increasing therapy effectiveness, cost-effectiveness of the screen and treat strategy improved. With the costs of pharmacological CCR5 blockade at the base–case level of €5057 per year or €421 per month, a RR for all-cause mortality of 0.82 or lower would cause the cost-effectiveness of the screen and treat strategy to be €50 or less per QALY gained. If the costs of CCR5 blockers drop, even a modest effectiveness in reducing inflammation-driven mortality would result in a treatment strategy that is good value for money.

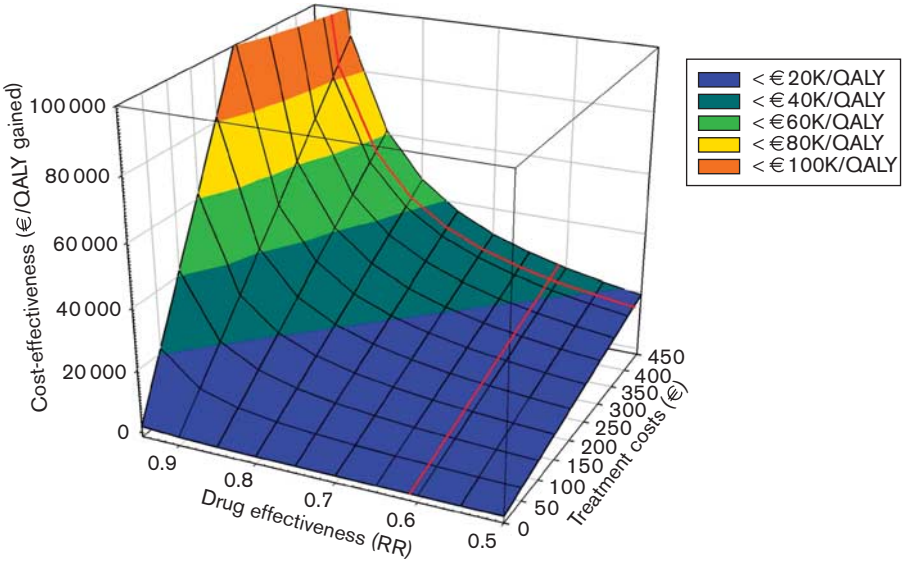
## Discussion

This study analyzed the potential cost-effectiveness of screening for the CCR5Δ32 polymorphism and selectively treating dialysis patients with the CCR5 insertion/insertion genotype and systemic inflammation with pharmacological CCR5 blockers. It was shown that such a strategy could be incorporated in a potentially cost-effective genetic screen and treat program.

Observational studies in which a genetic polymorphism is associated with a well-characterized functional phenotype can be considered as a type of clinical trial, with randomization at conception, referred to as Mendelian randomization [4–6]. Following this approach, we investigated the presumption that in an analogous manner, pharmacological CCR5 blockade could lead to better survival in ESRD patients and estimated the cost-effectiveness of a genetic screen and treat strategy based on this strategy. We used data from a genetic association study in ESRD patients. In this study an association with better survival was found in incident dialysis patients with systemic inflammation carrying the CCR5Δ32 genotype, which was replicated in a Swedish ESRD cohort, hereby showing the robustness of these findings. Moreover, as the number of patients in the CCR5Δ32 groups was small, we did in the previous study an analysis on the two cohorts combined, leading to the same results [19]. The presence of the CCR5Δ32 polymorphism, leading to a less functional receptor [14], was used as a naturalistic form of pharmacologically blocking the CCR5. This approach was used recently in cholesterol ester transfer protein inhibition, identifying alleles that lead to reduced CETP levels and activity [48]. Other cost-effectiveness assessments of potential pharmacologic interventions have previously been performed, for example in cardiovascular disease and polypill therapy [49]. Considering the ACCE (analytic validity, clinical validity, clinical utility and ethical, legal and social issues) model framework for enhancing the evaluation of genetic tests, this study adds to the second C by providing cost-effectiveness data that supports clinical utility [50,51].

A long-standing controversy in health economics is whether unrelated future costs should be included in cost-effectiveness analyses [40,41,52,53]. Dialysis treatment is expensive and associated with a high cost per

**Fig. 3**




Threshold analysis on the influence of CCR5 blocking therapy costs and effectiveness on the cost-effectiveness of a screen and treat strategy. The red lines denote the base–case parameters for drug effectiveness and treatment costs. QALY, quality-adjusted life years; RR, relative risk.

QALY gained [31,54]. As dialysis is required lifelong, the cost-effectiveness of therapies in ESRD patients has been said to be driven more by dialysis costs than by the costs and benefits of the intervention under consideration itself [55]. Our analysis confirms these earlier findings and underscores the relevance of the debate by calculating that inclusion of dialysis and renal transplant care costs double the ICER of the screen and treat strategy. Several studies in ESRD patients did not include the future costs of ESRD care [56–58], whereas others analysed therapies both with and without future costs [59–61]. By excluding ESRD costs in the main analysis but including them in a separate analysis our results can be widely compared. The cost-effectiveness with inclusion of future ESRD costs was comparable to other studies focusing on systemic anticoagulation [61], hyperphosphataemia [60], secondary hyperparathyroidism [59] and anaemia [62].

In addition to adherence to guidelines for pharmacoeconomic research as possible within the constraints of novel pharmacogenetic screening programs [22], this study had two major strengths: (i) the analyses considered hard endpoints, mortality and renal Tx; (ii) most primary data used in the pharmacoeconomic analysis, such as costs, QoL estimates and efficacy data were derived from a single prospectively followed dialysis cohort (NECOSAD). These strengths enhanced the clinical relevance and analytical robustness of the study findings. Although cost data used in this study were specific for the Netherlands, chronic kidney disease care costs such as dialysis costs have been reported to fall within a narrow range despite considerable variation in country of study, methodology and imputed costs [54]. Country-specific variations in drug costs and discounting rates have been accounted for in sensitivity analyses.

An important aspect of this study is the notion that equivalence between genetic effects and associated pharmacologic effectiveness is not a given fact. For example, a discordance has been described between the genetic effect of familial hypercholesterolaemia and the effectiveness of statin treatment on cardiovascular mortality [46]. The explanation for this discrepancy lies in the fact that genetic factors, as opposed to pharmacologic interventions, cause lifelong differences in risk factors [46]. Genetic factors are also not affected by traditional sources of uncertainty in clinical effectiveness, such as therapy compliance. Indeed, sensitivity analyses showed that the cost-effectiveness was highly influenced by the concordance between the genetic association and pharmacological effectiveness. Nevertheless, although the true effectiveness of pharmacological CCR5 blockade in ESRD patients on mortality is not (yet) known, this study, in particular the threshold analysis, provides valuable information for future clinical trials in this field. In this context, the threshold analysis showed that even modest pharmacological effectiveness would result in a treatment strategy that is good value for money. A similar approach has recently been taken in analyzing the potential cost-effectiveness of alternative treatments for patients with chronic kidney disease resistant to angiotensin I-converting enzyme inhibitors due to angiotensin I-converting enzyme (insertion/deletion) polymorphisms [36]. Finally, the robustness of the cost-effectiveness estimate depends on whether or not pharmacologically

blocking CCR5 is safe in patients with ESRD. However, treating HIV-infected patients with ESRD with a CCR5 antagonist seemed safe and no dose adjustments were necessary [63]. The next research step could be conducting an observational cohort study in HIV-infected patients with ESRD, to compare cardiovascular morbidity or mortality or surrogate endpoints such as intima media thickness, among users and nonusers of CCR5 blocker therapy.

In conclusion, we evaluated the potential cost-effectiveness of pharmacologically blocking the CCR5 receptor in inflamed dialysis patient with the CCR5 insertion/insertion genotype, and found it to be similar to existing treatment modalities for dialysis patients. Recently CCR5 blockade has indeed become feasible in humans. These data suggest that, from an economic point of view, it would be worthwhile to study whether pharmacological blockade of CCR5 has therapeutic and economical benefits in dialysis patients with persistent inflammation. Our study is an illustration of the potential of genetic studies in drug development programs, as a new source of Mendelian randomized evidence from an observational setting.

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The authors declare no conflict of interests.

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